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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/821,694	HILLIS, WILLIAM DANIEL	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-24,27-29 and 115-118* is/are pending in the application.

4a) Of the above claim(s) *16,17 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-15,18-24,27-31,36-39 and 115-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on February 17, 2004 has been entered. The claims pending in this application are claims 1, 6-24, 27-39, and 115-118 with claims 16, 17, and 32-35 withdrawn from consideration as the result of species election Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on February 17, 2004. Claims 1, 6-15, 18-24, 27-31, 36-39, and 115-118 will be examined.

Claim Objections

2. Claim 20 is objected to because of the following informality: "the hybridized nucleic acids" should be "the hybridized target nucleic acids" in order to correspond to claims 18 and 19.

3. Claim 39 is objected to because of the following informality: "enhance of hybridization" acids" should be "enhance hybridization" in order to correspond to claims 36 and 38.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 6-15, 18-24, 27-31, 36-39, and 115-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 1 is rejected as vague and indefinite because it is unclear what means "one overlapping nucleotide in common" and what kind of nucleotide in at least two oligonucleotide probes can be considered as an overlapping nucleotide in common. Please clarify.

7. Claim 10 recites the limitation "the oligonucleotide probe" in the claim. Since there are at least two oligonucleotide probes in claim 1 and an array of oligonucleotide probes in claim 7, it is unclear that the oligonucleotide probe is one of at least two oligonucleotide probes in claim 1 or one of an array of oligonucleotide probes in claim 7. Please clarify.

8. Claim 18 recites the limitation "hybridized target nucleic acid" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no phrase "hybridized target nucleic acid" in claim 1. Please clarify.

9. Claim 30 recites the limitation "each oligonucleotide probe" in the claim. Since there are at least two oligonucleotide probes in claim 1 and an array of oligonucleotide probes in claim 7, it is unclear that the oligonucleotide probe recited in claim 30 is one of at least two oligonucleotide probes in claim 1 or one of an array of oligonucleotide probes in claim 7. Please clarify.

10. Claim 32 recites the limitation "the common nucleic acid" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no phrase "common nucleic acid" in claims 1, 6, 7, and 16. Please clarify.

11. Claim 33 recites the limitation "the signature sequence" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no "signature sequence" in claims 1, 6, 7, 9, 14 and 30. Please clarify.

12. Claim 38 recites the limitation "the electric potential" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no "electric potential" in claims 1, 6, 7, 9, 14 and 29. Please clarify.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 1, 6, 18, 19, 23, and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Senapathy (US Paten No. 6,521,428, filed on November 4, 1999).

Note that this rejection was made in view of the ambiguity of claim 1.

Senapathy teaches shot-gun sequencing and amplification without cloning. In the method of sequencing a nucleic acid template, the method steps comprise: (a) providing a plurality of first primers, each first primer comprising (1) a region of different fixed nucleotide sequence having a defined length of from about 5 to 15 bases long and (ii) a region of randomized nucleotide sequence having a defined length of from about 2 to 11 bases long located 5' to or 3' to the region of fixed nucleotide sequence and a handle at an end of each first primer wherein the handle is one or more universal bases; (b) annealing the plurality of first primers to different locations on a nucleic acid template (ie., genomic DNA or cDNA), wherein at least one primer from the plurality of first primers anneal specifically to the template; (c) extending the

specifically annealed primer from step b) with a mixture of dNTPs and ddNTPs to generate a series of nucleic acid fragments; and (d) determining the nucleotide sequence of a first region of the template from the series of nucleic acid fragments (see first paragraph in column 5 and claims 19-24 in columns 25 and 26).

Regarding claims 1, 23, and 24, since Senapathy teaches that each first primer comprises a region of different fixed nucleotide sequence having a defined length of from about 5 to 15 bases long, a region of randomized nucleotide sequence having a defined length of from about 2 to 11 bases long located 5' to or 3' to the region of fixed nucleotide sequence and a handle at an end of each first primer wherein the handle is one or more universal bases and the universal base is capable of base pairing with either a purine or pyrimidine, and claim 1 does not limit positions of one overlapping nucleotide in common and at least one variable nucleotide, any nucleotide in each first primer that is complementary to the nucleic acid template is a variable nucleotide as recited in claim 1 and one nucleotide (ie., A or G or C or T) that can be found in each first primer is a nucleotide in common as recited in claim 1. Since at least two first primers anneal to different locations on a nucleic acid template and any nucleotide in each first primer that is complementary to the nucleic acid template is a variable nucleotide, Senapathy discloses contacting the analyte, under hybridizing conditions, with at least two oligonucleotide probes that have at least one overlapping nucleotide in common and at least one variable nucleotide wherein hybridization of the at least two oligonucleotide probes to the target sequence segment occurs only if the at least one variable nucleotide of the at least two oligonucleotide probes base pairs with a corresponding nucleotide on the target sequence segment as recited in claim 1.

Therefore, claim 1 is anticipated by Senapathy. Since genomic DNA or cDNA are used as a nucleic acid template, claims 23 and 24 are anticipated by Senapathy.

Regarding claim 6, since the method taught by Senapathy is used for sequencing a nucleic acid template, claim 6 is anticipated by Senapathy.

Regarding claims 18 and 19, in the method for amplifying a nucleic acid template, the method steps comprises: (a) providing a plurality of first primers, each first primer comprising (i) a region of different fixed nucleotide sequence having a defined length of from about 5 to 15 bases long and (ii) a region of randomized nucleotide sequence having a defined length of from about 2 to 11 bases long located 5' to or 3' to the region of fixed nucleotide sequence; (b) providing a plurality of second primers, each second primer comprising (i) a region of different fixed nucleotide sequence having a defined length of from about 5 to 15 bases long and (ii) a region of randomized nucleotide sequence having a defined length of from about 2 to 11 bases long located 5' to or 3 ' to the region of fixed nucleotide sequence, wherein the regions of fixed nucleotide sequence in the second plurality of primers is shorter than the regions of fixed nucleotide sequence in the first plurality of primers; and (c) amplifying a first region of the nucleic acid template with the plurality of first primers and the plurality of second primers, wherein at least one primer from within each of the plurality of first primers and the plurality of second primers anneal specifically to the template (see lines 5-15 in column and claim 25 in column 26). Since a polymerase chain reaction is performed in the presence of a polymerase using at least a pair of primers, claims 18 and 19 are anticipated by Senapathy.

Regarding claim 115, since, as shown in claim 1, any nucleotide in each first primer that is complementary to the nucleic acid template taught by Senapathy is a variable nucleotide and

the universal base is capable of base pairing with either a purine or pyrimidine, Senapathy discloses that the variable nucleotide (ie., universal base) of at least one of the at least two oligonucleotide probes (ie., two first primers taught by Senapathy) is a degenerately pairing nucleotide analog as recited in claim 115.

Regarding claim 117, since any nucleotide in each first primer that is complementary to the nucleic acid template taught by Senapathy is a variable nucleotide, the nucleic acid template taught by Senapathy is any kind of nucleic acid such as cDNA or a RNA (see column 5, first paragraph) and at least one of A, T, C, and G in each first primer can hybridize with cDNA template, Senapathy discloses that the target nucleic acid analyte is DNA and the variable nucleotide of the at least two oligonucleotide probes is independently selected from the group consisting of A, T, C, and G as recited in claim 117.

Regarding claim 118, since any nucleotide in each first primer that is complementary to the nucleic acid template taught by Senapathy is a variable nucleotide, the nucleic acid template taught by Senapathy is any kind of nucleic acid such as cDNA or a RNA (see column 5, first paragraph) and at least one of A, T, C, and G in each first primer can hybridize with RNA template, Senapathy discloses that the target nucleic acid analyte is RNA and the variable nucleotide of the at least two oligonucleotide probes is independently selected from the group consisting of A, U, C, or G as recited in claim 118.

Therefore, Senapathy teaches all limitations recited in claims 1, 6, 18, 19, 23, 24, 115, 117, and 118.

Response to Arguments

In page 11, second paragraph of applicant's remarks, applicant argues that "[S]enapathy does not teach or suggest a method for using at least two oligonucleotide probes with at least one nucleotide overlap and at least one variable position to obtain information on a target nucleic acid analyte with a target sequence segment, wherein hybridization does not occur where there is a mismatch at the variable position of the oligonucleotide primers,".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. Since any nucleotide in each first primer that is complementary to the nucleic acid template taught by Senapathy is a variable nucleotide as recited in claim 1 and one nucleotide (ie., A or G or C or T) that can be found in each first primer taught by Senapathy is a nucleotide in common as recited in claim 1, and, in the method of sequencing a nucleic acid template, Senapathy teaches (a) providing a plurality of first primers, each first primer comprising (i) a region of different fixed nucleotide sequence having a defined length of from about 5 to 15 bases long and (ii) a region of randomized nucleotide sequence having a defined length of from about 2 to 11 bases long located 5' to or 3' to the region of fixed nucleotide sequence and a handle at an end of each first primer wherein the handle was one or more universal bases; (b) annealing the plurality of first primers to different locations on a nucleic acid template (ie., genomic DNA or cDNA), wherein at least one primer from within the plurality of first primers annealed specifically to the template; (c) extending the specifically annealed primer from step b) with a mixture of dNTPs and ddNTPs to generate a series of nucleic acid fragments; and (d) determining the nucleotide sequence of a first region of the template from the series of nucleic acid fragments (see first paragraph in column 5 and claims 19-24 in columns 25 and 26),

Senapathy teaches a method for using at least two oligonucleotide probes with at least one nucleotide overlap and at least one variable position to obtain information on a target nucleic acid analyte with a target sequence segment.

15. Claims 1, 6, 7, 9-15, 17, 21-24, 27, 29-31, 33-35, 38, 115, 117, and 118 are rejected under 35 U.S.C. 102(e) as being anticipated by Drmanac *et al.*, (US Patent No. 6,297,006, priority date: October 2, 2001).

Note that this rejection was made in view of the ambiguity of claim 1.

Drmanac *et al.*, teach methods for sequencing repetitive sequences and for determining the order of sequence subfragments.

Regarding claim 1, Drmanac *et al.*, teach a method for detecting a target nucleic acid specie including the steps of providing an array of probes affixed to a substrate and a plurality of labeled probes wherein each labeled probe is selected to have a first nucleic acid sequence which is complementary to a first portion of a target nucleic acid and wherein the nucleic acid sequence of at least one probe affixed to the substrate is complementary to a second portion of the nucleic acid sequence of the target, the second portion being adjacent to the first portion; applying a target nucleic acid to the array under suitable conditions for hybridization of probe sequences to complementary sequences; introducing a labeled probe to the array; hybridizing a probe affixed to the substrate to the target nucleic acid; hybridizing the labeled probe to the target nucleic acid; affixing the labeled probe to an adjacently hybridized probe in the array; and detecting the labeled probe affixed to the probe in the array wherein the array of probes affixed to the substrate comprises a universal set of probes (see column 2, third paragraph). Since claim 1 does not limit

positions of one overlapping nucleotide in common and at least one variable nucleotide, any nucleotide in an array of probes affixed to a substrate and a plurality of labeled probes that is complementary to the target nucleic acid taught by Drmanac *et al.*, is a variable nucleotide as recited in claim 1 and one nucleotide (ie., A or G or C or T) that can be found in an array of probes affixed to a substrate and a plurality of labeled probes is a nucleotide in common as recited in claim 1. Therefore, Drmanac *et al.*, disclose contacting the analyte (ie., the target nucleic acid taught by Drmanac *et al.*,), under hybridizing conditions, with at least two oligonucleotide probes (ie., an array of probes affixed to a substrate and a plurality of labeled probes) that have at least one overlapping nucleotide in common and at least one variable nucleotide wherein hybridization of the at least two oligonucleotide probes to the target sequence segment occurs only if the at least one variable nucleotide of the at least two oligonucleotide probes base pairs with a corresponding nucleotide on the target sequence segment as recited in claim 1.

Regarding claims 6, 7, 10, 11, and 27, since the method taught by Drmanac *et al.*, is used to sequencing repetitive sequences and for determining the order of sequence subfragments (see Title of this patent), Drmanac *et al.*, disclose that the method of claim l can be used for sequencing the target nucleic acid analyte as recited in claim 6. Drmanac *et al.*, also teach that a sample nucleic acid is sequenced by exposing the sample to a support-bound probe of known sequence and a labeled probe or probes in solution. Wherever the probes ligase is introduced into the mixture of probes and sample, such that, wherever a support has a bound probe and a labeled probe hybridized back to back along the sample, the two probes are chemically linked by the action of the ligase. After washing, only chemically linked support-bound and labeled probes are

detected by the presence of the labeled probe. By knowing the identity of the support-bound probe at a particular location in an array, and the identity of the labeled probe, a portion of the sequence of the sample is determined (see column 47, last paragraph bridging to column 48, first paragraph). Based on above teachings, Drmanac *et al.*, disclose that the method of claim 6 further comprising an array of oligonucleotide probes wherein the sequence of the target nucleic acid analyte is determined by analysis of hybridization data obtained from the array of oligonucleotide probes as recited in claim 7 wherein the sequencing method is by detection of labels that attach by hybridization to the target sequence segment as recited in claim 17 and the sequencing method is by analysis of hybridization data obtained from an array of target nucleic acid analyte sequences attached to a substrate surface as recited in claim 27. Since Drmanac *et al.*, teach that, after washing, only chemically linked support-bound and labeled probes are detected by the presence of the labeled probe (see column 47, last paragraph bridging to column 48, first paragraph), Drmanac *et al.*, disclose the target sequence segment (ie., the target nucleic acid taught by Drmanac *et al.*,) hybridized to the oligonucleotide probe (ie., an array of probes affixed to a substrate taught by Drmanac *et al.*,) is detected by a discrete label moiety linked to the target sequence segment (ie., the labeled probe is linked to the target nucleic acid after the hybridization) wherein the discrete label moiety linked to the target sequence segment comprises a nucleic acid sequence (ie., one of a plurality of labeled probes taught by Drmanac *et al.*,) as recited in claims 10 and 11.

Regarding claims 9 and 29, since Drmanac *et al.*, teach that the array is a 96-well plate with 96 identical subarray (ie., identical oligonucleotide probes) (see example 11, four paragraph), Drmanac *et al.*, disclose that the array comprises a substrate having a surface, the

surface having a plurality of discrete surface sites, each site having attached a plurality of oligonucleotide probes of identical sequence as recited in claims 9 and 29.

Regarding claims 12-15, Drmanac *et al.*, teach that the discrete label moiety linked to the target sequence segment comprises a luminescent moiety wherein the luminescent moiety is a chemiluminescent or fluorescent moiety as recited in claims 12 and 13, and the target sequence segment is detected by a target signal wherein the target signal is ^{32}P (see column 8, lines 47-50).

Regarding claims 21 and 22, since the method taught by Drmanac *et al.*, is used in genetic mapping for alleles (see column 51), claims 21 and 22 are anticipated by Drmanac *et al.*.

Regarding claims 23 and 24, since the target nucleic acids to be sequenced taught by Drmanac *et al.*, are obtained from any appropriate source such as cDNAs, genomic DNA (see column 19, fourth paragraph), claims 23 and 24 are anticipated by Drmanac *et al.*.

Regarding claims 30, 31, and 33-35, Drmanac *et al.*, teach that a pool of multiple labeled probes selected to specifically bind to the target sequences adjacent to the immobilized probes (see column 55, fourth paragraph), Drmanac *et al.*, disclose that each oligonucleotide probe sequence (ie., a pool of multiple labeled probes) additionally comprises a linker moiety (ie., a region that binds to the target sequence and is far from the label) and a label moiety (ie., a region that binds to the target sequence with a label on one of a pool of multiple labeled probes) as recited in claim 30 wherein the linker moiety comprises a common nucleic acid sequence (ie., A or T or G or C) and the label moiety comprises a signature nucleic acid sequence (ie., a region that binds to the target sequence and is close to a labels on one of a pool of multiple labeled probes) that identifies the target sequence segment as recited in claim 31. Since Drmanac *et al.*, teach that the signal of the labeled probes are amplified by binding to a further probe agent

which is multiply labeled (see column 55, fifth paragraph), Drmanac *et al.*, disclose that the array is imaged with decoder labels comprising a nucleic aid sequence complementary to the signature sequence and a second label moiety as recited in claim 33. Since the multiply labels can be chromogenic labels (see column 55, fifth paragraph) that include fluorescent or chemiluminescent moiety (see column 8, lines 47-50), claims 34 and 35 are anticipated by Drmanac *et al.*.

Regarding claim 38, since Drmanac *et al.*, teach that the vertical electric field helps to restrict movement of the samples and prevents diffusion of the sorted targets during the process of target sorting (see column 28, fourth paragraph), Drmanac *et al.*, teach that the electric potential at the substrate surface is electronically controlled to enhance hybridization as recited in claim 38.

Regarding claim 115, since, as shown above, any nucleotide in an array of probes affixed to a substrate and a plurality of labeled probes that is complementary to the target nucleic acid taught by Drmanac *et al.*, is a variable nucleotide and the array of probes affixed to the substrate comprises a universal set of probes (see column 2, last paragraph), Drmanac *et al.*, disclose that the variable nucleotide of at least one of the at least two oligonucleotide probes (ie., an array of probes affixed to a substrate) is a degenerately pairing nucleotide analog as recited in claim 115.

Regarding claim 117, since any nucleotide in an array of probes affixed to a substrate and a plurality of labeled probes that is complementary to the target nucleic acid taught by Drmanac *et al.*, is a variable nucleotide and the nucleic acid template taught by Drmanac *et al.*, is any kind of nucleic acid such as cDNA or a RNA (see column 19, fourth paragraph) and at least one of A, T, C, and G in the array of probes can hybridize with the cDNA template, Drmanac *et al.*,

disclose that the target nucleic acid analyte is DNA and the variable nucleotide of the at least two oligonucleotide probes is independently selected from the group consisting of A, T, C, and G as recited in claim 117.

Regarding claim 118, since any nucleotide in an array of probes affixed to a substrate and a plurality of labeled probes that is complementary to the target nucleic acid taught by Drmanac *et al.*, is a variable nucleotide and the nucleic acid template taught by Drmanac *et al.*, is any kind of nucleic acid such as cDNA or a RNA (see column 19, fourth paragraph) and at least one of A, U, C, and G in the array of probes can hybridize with the RNA template, Drmanac *et al.*, disclose that the target nucleic acid analyte is RNA and the variable nucleotide of the at least two oligonucleotide probes is independently selected from the group consisting of A, U, C, or G as recited in claim 118.

Therefore, Drmanac *et al.*, teach all limitation of claims 1, 6, 7, 9-15, 17, 21-24, 27, 29-31, 33-35, 38, 115, 117, and 118.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Senapathy (1999) as applied to claims 1, 6, 18, 19, 23, 24, 115, 117, and 118 above, and further in view of Santamaria *et al.*, (US Patent No.5, 578, 443, published on November 26, 1996).

The teachings of Senapathy have been summarized previously, *supra.*

Senapathy does not disclose to use his method for a genetic analysis such as allelic analysis as recited in claims 21 and 22.

Santamaria *et al.*, teach DNA sequence-based HLA typing method. Their PCR and sequencing methods are used for a genetic analysis such as allelic analysis (see lines 9-47 in column 2 and lines 14-21 in column 4).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used the method recited in claim 1 for a genetic analysis (ie., allelic analysis) in view of the patents of Senapathy and Santamaria *et al.*. One having ordinary skill in the art would have been motivated to do so because Santamaria *et al.*., have successfully used a sequencing method for a genetic analysis (ie., allelic analysis) and the simple replacement of one kind of sequencing method (i.e., the sequencing method taught by Santamaria *et al.*,) from another kind of sequencing method (i.e., the sequencing method taught by Senapathy) for a genetic analysis would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the sequencing method taught by Senapathy and the sequencing method taught by Santamaria *et al.*, are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Response to Arguments

In page 11, last paragraph of applicant's remarks, applicant argues that "[B]ecause the primary reference, Senapathy, does not anticipate or render obvious the claimed invention as recited in claim 1, the additional teachings of Santamaria et al. cannot serve to render the invention of claims 21 and 22 obvious. Accordingly, since the hypothetical combination of Senapathy in view of Santamaria et al. does not render the claimed invention obvious, applicants respectfully request reconsideration and withdrawal of this rejection.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, Senapathy, does anticipate the claimed invention as recited in claim 1 (see above argument on the rejection under 35 USC 102 (e)); and (2) applicant does not explain why the additional teachings of Santamaria et al., cannot serve to render the invention of claims 21 and 22 obvious.

18. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac *et al.*, as applied to claims 1, 6, 7, 9-15, 17, 21-24, 27, 29-31, 33-35, 38, 115, 117, and 118 above, and further in view of Vesnaver *et al.*, (Proc. Natl. Acad. Sci. USA, 88, 3569-3573, May 1991).

The teachings of Drmanac *et al.*, have been summarized previously, *supra.*

Drmanac *et al.*, do not teach that detection of a target sequence segment hybridizing to an

oligonucleotide probe is by detection of the heat of hybridization as recited in claim 16.

Vesnaver *et al.*, teach the contribution of DNA single-stranded order to the thermodynamics of duplex formation.

Regarding claim 16, since Vesnaver *et al.*, teach to detect duplex formation by comparing entropies of a single stranded nucleic acid and a double stranded nucleic acid (see page 3569, abstract and Table 2 in page 3571), Vesnaver *et al.*, disclose that detection of a target sequence segment hybridizing to an oligonucleotide probe is by detection of the heat of hybridization (ie., entropies of a single stranded nucleic acid and a double stranded nucleic acid) as recited in claim 16.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used the method recited in claim 16 wherein detection of a target sequence segment hybridizing to an oligonucleotide probe is by detection of the heat of hybridization in view of the prior art of Drmanac *et al.*, and Vesnaver *et al.*. One having ordinary skill in the art would have been motivated to do so because Vesnaver *et al.*, suggest to study the formation of duplexes and higher-order DNA structure (e.g., triplexes, tetraplexes, etc.) from their component single strands using isothermal titration such as comparing entropies of a single stranded nucleic acid and a double stranded nucleic acid (see page 3569, abstract) and the simple replacement of one kind of detection method (i.e., the detection method taught by Drmanac *et al.*,) from another kind of detection method (i.e., the detection method taught by Vesnaver *et al.*,) during the process of detecting hybridization, would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the detection method

taught by Drmanac *et al.*, and the detection method taught by Vesnaver *et al.*, are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

19. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac *et al.*, as applied to claims 1, 6, 7, 9-15, 17, 21-24, 27, 29-31, 33-35, 38, 115, 117, and 118 above, and further in view of Dattagupta (US Patent No. 5,215,899, published on June 1, 1993).

The teachings of Drmanac *et al.*, have been summarized previously, *supra.*

Drmanac *et al.*, do not disclose that the hybridized nucleic acids are amplified by a RNA replicase enzyme as recited in claim 20.

Dattagupta teaches, upon hybridization with a target sequence complementary to the probe sequence, the target sequence is transcripted in the presence of a suitable RNA polymerase (ie., a RNA replicase enzyme) and appropriate ribonucleoside triphosphate (rNTPs) (see abstract).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 20 wherein the hybridized nucleic acids are amplified by a RNA replicase enzyme in view of the patents of Drmanac *et al.*, and Dattagupta. One having ordinary skill in the art would have been motivated to do so because Dattagupta has successfully amplified a target sequence in a complex formed by

the target sequence and a probe sequence and amplification of the target sequence in the complex formed by the target sequence and the probe sequence would allow transcription to proceed until a desired amount of RNA transcription product has accumulated (see abstract). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to amplify the hybridized nucleic acids recited in claim 20 by a RNA replicase enzyme.

20. Claims 8, 28, 36, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac *et al.*, as applied to claims 1, 6, 7, 9-15, 17, 21-24, 27, 29-31, 33-35, 38, 115, 117, and 118 above, and further in view of Walt *et al.*, (US 2001/0029049 A1, filed on April 6, 1999).

The teachings of Drmanac *et al.*, have been summarized previously, *supra.* Since Drmanac *et al.*, teach that hybridization and washing conditions are selected to detect substantially perfect match hybrids or are selected to permit detection only of perfect match hybrids by the use of more stringent hybridization conditions (see column 8, lines 17-22), Drmanac *et al.*, disclose that the hybridization is enhanced by increasing hybridization stringency as recited in claim 37.

Drmanac *et al.*, disclose that the array comprises arrayed individual beads or particles, each bead or particle having a surface to which is attached a plurality of oligonucleotide probes of identical sequence as recited in claims 8 and 28, and the substrate surface is functionalized with a surface modification to enhance hybridization as recited in claim 36.

Walt *et al.*, teach that the array comprises arrayed individual beads or particles, each bead

or particle having a surface to which is attached a plurality of oligonucleotide probes of identical sequence as recited in claims 8 and 28. Since this array having beads attached a plurality of oligonucleotide probes of identical sequence has the ability to make quantitative estimates of confidence about the data and significant increases in sensitivity (see page 19, [0176]), Walt *et al.*, teach that the substrate surface (ie., the surface of the array) is functionalized with a surface modification (ie., the modification with beads) to enhance hybridization as recited in claim 36.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 wherein the array comprises arrayed individual beads or particles, each bead or particle having a surface to which is attached a plurality of oligonucleotide probes of identical sequence as recited in claims 8 and 28 in order to enhance hybridization as recited in claim 36 in view of the patents of Drmanac *et al.*, and Walt *et al.*. One having ordinary skill in the art would have been motivated to do so because Walt *et al.*, have successfully made the array comprises arrayed individual beads or particles wherein each bead or particle having a surface to which is attached a plurality of oligonucleotide probes of identical sequence and suggest that the array having beads attached a plurality of oligonucleotide probes of identical sequence has the ability to make quantitative estimates of confidence about the data and significant increases in sensitivity (see page 19, [0176]). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to make an array comprises arrayed individual beads or particles wherein each bead or particle having a surface to which is attached a plurality of oligonucleotide probes of identical sequence in order to enhance hybridization.

21. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac *et al.*, as applied to claims 1, 6, 7, 9-15, 17, 21-24, 27, 29-31, 33-35, 38, 115, 117, and 118 above, and further in view of Ackley (US Patent No. 5,728,532, published on March 17, 1998).

The teachings of Drmanac *et al.*, have been summarized previously, *supra.* Since Drmanac *et al.*, teach that oligonucleotides are immobilized on a support selected from a glass, nylon, silicon and fluorocarbon supports (see column 8, lines 58-63), Drmanac *et al.*, disclose an integrated substrate comprising a semiconductor chip (ie., a silicon support) as recited in claim 39.

Drmanac *et al.*, do not disclose the integrated substrate comprising electronic circuitry wherein the electric potential at the individual array sites of the substrate surface is independently electronically controlled to enhance hybridization as recited in claim 39.

Ackley teaches electrode configuration for matrix addressing of a molecular detection device.

Regarding claim 39, Ackley teaches a DNA chip having an array of selective binding sites each having respective single-stranded DNA probes. During hybridization, a target DNA attaches to one or more of the DNA probes. To hasten the hybridization process, a local concentration of target DNA is increased at predetermined sites using electric field enhancements. Each site has an electrode associated therewith for selectively generating an electric field thereby. The electric field is generated by applying an electric potential difference between an electrode at the site and a counter electrode at a peripheral portion of the chip. To attract DNA fragments to the site, the polarity of the electric potential difference is selected to generate an electric field having a polarity opposite to the charge of the DNA fragments (see

column 1, third and fourth paragraphs). Based on above teachings, Ackley discloses the integrated substrate comprising electronic circuitry (ie., electrode) wherein the electric potential at the individual array sites of the substrate surface is independently electronically controlled to enhance hybridization as recited in claim 39.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used the method recited in claim 29 using an integrated substrate having a semiconductor chip comprising electronic circuitry (ie., electrode) wherein the electric potential at the individual array sites of the substrate surface is independently electronically controlled to enhance hybridization in view of the patents of Drmanac *et al.*, and Ackley. One having ordinary skill in the art would have been motivated to do so because, to enhance hybridization process, Ackley teaches to use an integrated substrate comprising electronic circuitry (ie., electrode) wherein the electric potential at the individual array sites of the substrate surface is independently electronically controlled (see column 1, fourth and fifth paragraphs). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to use an integrated substrate comprising electronic circuitry (ie., electrode) wherein the electric potential at the individual array sites of the substrate surface is independently electronically controlled to enhance hybridization.

22. Claim 116 is rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac *et al.*, as applied to claims 1, 6, 7, 9-15, 17, 21-24, 27, 29-31, 33-35, 38, 115, 117, and 118 above, and further in view of Hill *et al.*, (Proc. Natl. Acad. Sci. USA, 95, 4258-4263, April 1998).

The teachings of Drmanac *et al.*, have been summarized previously, *supra.*

Drmanac *et al.*, do not disclose that the degenerately pairing nucleotide analog is dPTP as recited in claim 116 although Drmanac *et al.*, teach that universal base can be dMTP (see column 12, fourth paragraph).

Hill *et al.*, teach to perform PCR and DNA sequencing using oligonucleotides having dPTP (see page 4260 and Figures 3 and 4).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used the method recited in claim 116 wherein the degenerately pairing nucleotide analog is dPTP in view of the patents of Drmanac *et al.*, and Hill *et al.*. One having ordinary skill in the art would have been motivated to do so because dPTP only binds to pyrimidine bases and does not bind to purine bases, and use of dPTP as an universal base in degenerate oligonucleotides would significantly reduce the complexity of these primers (see page 4258, abstract) and the simple replacement of one kind of universal base (i.e., the universal bases taught by Drmanac *et al.*,) from another kind of universal base (i.e., dPTPs taught by Hill *et al.*,) during the process for performing the method recited in claim 116, would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955.

Conclusion

23. No claim is allowed.

24. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703)872-9306 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
April 28, 2004

FRANK LU
PATENT EXAMINER